Clinical trial results:
A trial comparing the effect and safety of insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes.

Summary

EudraCT number	2017-000048-17
Trial protocol	DK GB AT IE GR ES HR IT
Global end of trial date	17 December 2020

Results information

Result version number	v1 (current)
This version publication date	25 December 2021
First version publication date	25 December 2021

Trial information

Trial identification

Sponsor protocol code	NN1250-4300

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03377699
WHO universal trial number (UTN)	U1111-1191-3018

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Transparency Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Transparency Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2020
Global end of trial reached?	Yes
Global end of trial date	17 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect on glycaemic control of insulin degludec once daily plus insulin aspart 2-4 times daily with meals and insulin detemir once daily or twice daily plus insulin aspart 2-4 times daily with meals in a population of pregnant women with type 1 diabetes mellitus.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Last amended by the 64th World Medical Association General Assembly, Fortaleza, Brazil. October 2013) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents (Nov 2016) and 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	22 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Brazil: 31
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Russian Federation: 67
Country: Number of subjects enrolled	Serbia: 14
Worldwide total number of subjects	225
EEA total number of subjects	51

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	225
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 56 sites in 14 countries as follows (number of sites that screened subjects/ number of sites that randomised subjects):Argentina (5/4); Australia (7/7); Austria (3/3); Brazil (6/6); Canada (6/5); Croatia (1/1); Denmark (2/2); Greece (3/3); Ireland (3/2); Israel (2/2); Italy (5/5); Russia (8/8); Serbia (2/2) and UK (8/6).

Pre-assignment

Screening details:

Based on subject pregnancy status, either non-pregnant with the intention to become pregnant or pregnant from gestational Week (GW) 8-13 + 6 days were randomised in a 1:1 ratio to receive either Insulin Degludec (IDeg) or Insulin Detemir (IDet) in combination with Insulin Aspart (IAsp) as subcutaneous injection.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	IDeg

Arm description:

Subjects were to receive IDeg once daily in combination with IAsp 2-4 times daily with meals as subcutaneous injection using FlexTouch and FlexPen pen injectors respectively. After randomization, the IDeg doses were adjusted once weekly to reach the glycaemic target of 4.0 – 5.0 millimoles per liter (mmol/L). It was based on mean of 3 pre-breakfast self-measured plasma glucose (SMPG) values measured on 2 days prior to visit and on the day of the visit. If one of the SMPG values was below target of 4.0 mmol/L, the insulin dose was reduced: (less than) <3.1: -4 units (U) and 3.1 – 3.9: -2U. If the mean was: 4.0-5.0: no adjustment; 5.1 – 10.0: +2U, 10.1 – 15.0: +4U and (greater than) >15.0: +6U. On the other hand, for pregnant women, the SMPG was measured 60 minutes after main meal and the IAsp doses were optimized at investigator's discretion based on the subject's SMPG values with target value (less than or equal to) ≤7.8 mmol/L.

Arm type	Experimental
Investigational medicinal product name	Insulin Degludec
Investigational medicinal product code	
Other name	Tresiba®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were to receive IDeg once daily with meals as subcutaneous injection using FlexTouch pen injector. After randomization, the IDeg doses were adjusted once weekly to reach the glycaemic target of 4.0 – 5.0 mmol/L. It was based on mean of 3 pre-breakfast SMPG values measured on 2 days prior to visit and on the day of the visit. If one of the SMPG values was below target of 4.0 mmol/L, the insulin dose was reduced: (less than) <3.1 mmol/L: -4 units (U) and 3.1 – 3.9 mmol/L: -2U. If the mean was: 4.0-5.0 mmol/L: no adjustment; 5.1 – 10.0 mmol/L: +2U, 10.1 – 15.0 mmol/L: +4U and (greater than) >15.0 mmol/L- +6U.

Investigational medicinal product name	IAsp
Investigational medicinal product code	
Other name	NovoRapid®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were to receive IAsp, 2-4 times daily with meals as subcutaneous injection using FlexPen pen injector. After randomization, the IAsp dose adjustments were at investigator's discretion based on the

subject's SMPG values. For pregnant women, the SMPG was measured 60 minutes after main meal and the IAsp doses were optimized with target SMPG value ≤ 7.8 mmol/L.

Arm title	IDet

Arm description:

Subjects were to receive IDet once or twice daily in combination with IAsp 2-4 times daily with meals as subcutaneous injection using FlexPen pen injector. The dose adjustments were made with a glycaemic target of 4.0 – 5.0 mmol/L. Dose adjustments: for IDet once daily - based on mean of 3 pre-breakfast SMPG values; for IDet twice daily - morning doses - based on mean pre-main evening meal SMPG values whereas the evening doses - based on mean pre-breakfast SMPG values. If one of the pre-main evening meal SMPG values were below target of 4.0 mmol/L, the insulin dose was reduced: <3.1 mmol/L: -4U and 3.1 – 3.9 mmol/L: -2U. If the mean was: 4.0-5.0 mmol/L- no adjustment; 5.1 – 10.0 mmol/L: +2U, 10.1 – 15.0 mmol/L: +4U and >15.0 mmol/L: +6U. For pregnant, the SMPG was measured 60 minutes after main meal and the IAsp doses were optimized at investigator's discretion based on the subject's SMPG values with target value ≤7.8 mmol/L.

Arm type	Active comparator
Investigational medicinal product name	IDet
Investigational medicinal product code	
Other name	Levemir®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received IDet once or twice daily in combination with IAsp 2-4 times daily with meals as subcutaneous injection. Dose adjustments were made with glycaemic target of 4.0–5.0 mmol/L. Dose adjustments: for IDet once daily - based on mean of 3 pre-breakfast SMPG values; for IDet twice daily - morning doses - based on mean pre-main evening meal SMPG values whereas the evening doses - based on mean pre-breakfast SMPG values. If one of the pre-main evening meal SMPG values were below target of 4.0 mmol/L, the insulin dose was reduced: <3.1: -4U and 3.1 – 3.9: -2U. If the mean was: 4.0-5.0 mmol/L- no adjustment; 5.1 – 10.: +2U, 10.1 – 15.0: +4U and >15.0: +6U.

Investigational medicinal product name	IAsp
Investigational medicinal product code	
Other name	NovoRapid®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were to receive IAsp, 2-4 times daily with meals as subcutaneous injection using FlexPen pen injector. After randomization, the IAsp dose adjustments were at investigator's discretion based on the subject's SMPG values. For pregnant women, the SMPG was measured 60 minutes after main meal and the IAsp doses were optimized with target SMPG value ≤ 7.8 mmol/L.

Number of subjects in period 1	IDeg	IDet
Started	111	114
Completed	89	89
Not completed	22	25
Consent withdrawn by subject	2	9
Unclassified	19	15
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	IDeg

Reporting group description:

Subjects were to receive IDeg once daily in combination with IAsp 2-4 times daily with meals as subcutaneous injection using FlexTouch and FlexPen pen injectors respectively. After randomization, the IDeg doses were adjusted once weekly to reach the glycaemic target of 4.0 – 5.0 millimoles per liter (mmol/L). It was based on mean of 3 pre-breakfast self-measured plasma glucose (SMPG) values measured on 2 days prior to visit and on the day of the visit. If one of the SMPG values was below target of 4.0 mmol/L, the insulin dose was reduced: (less than) <3.1: -4 units (U) and 3.1 – 3.9: -2U. If the mean was: 4.0-5.0: no adjustment; 5.1 – 10.0: +2U, 10.1 – 15.0: +4U and (greater than) >15.0: +6U. On the other hand, for pregnant women, the SMPG was measured 60 minutes after main meal and the IAsp doses were optimized at investigator's discretion based on the subject's SMPG values with target value (less than or equal to) ≤7.8 mmol/L.

Reporting group title	IDet

Reporting group description:

Subjects were to receive IDet once or twice daily in combination with IAsp 2-4 times daily with meals as subcutaneous injection using FlexPen pen injector. The dose adjustments were made with a glycaemic target of 4.0 – 5.0 mmol/L. Dose adjustments: for IDet once daily - based on mean of 3 pre-breakfast SMPG values; for IDet twice daily - morning doses - based on mean pre-main evening meal SMPG values whereas the evening doses - based on mean pre-breakfast SMPG values. If one of the pre-main evening meal SMPG values were below target of 4.0 mmol/L, the insulin dose was reduced: <3.1 mmol/L: -4U and 3.1 – 3.9 mmol/L: -2U. If the mean was: 4.0-5.0 mmol/L- no adjustment; 5.1 – 10.0 mmol/L: +2U, 10.1 – 15.0 mmol/L: +4U and >15.0 mmol/L: +6U. For pregnant, the SMPG was measured 60 minutes after main meal and the IAsp doses were optimized at investigator's discretion based on the subject's SMPG values with target value ≤7.8 mmol/L.

Reporting group values	IDeg	IDet	Total
Number of subjects	111	114	225
Age Categorical Units: Subjects			
Adults (18-64 years)	111	114	225
Age Continuous Units: years			
arithmetic mean	31.2	31.1	
standard deviation	± 5.20	± 5.28	-
Gender Categorical Units: Subjects			
Female	111	114	225

End points

End points reporting groups

Reporting group title	IDeg

Reporting group description:

Subjects were to receive IDeg once daily in combination with IAsp 2-4 times daily with meals as subcutaneous injection using FlexTouch and FlexPen pen injectors respectively. After randomization, the IDeg doses were adjusted once weekly to reach the glycaemic target of 4.0 – 5.0 millimoles per liter (mmol/L). It was based on mean of 3 pre-breakfast self-measured plasma glucose (SMPG) values measured on 2 days prior to visit and on the day of the visit. If one of the SMPG values was below target of 4.0 mmol/L, the insulin dose was reduced: (less than) <3.1: -4 units (U) and 3.1 – 3.9: -2U. If the mean was: 4.0-5.0: no adjustment; 5.1 – 10.0: +2U, 10.1 – 15.0: +4U and (greater than) >15.0: +6U. On the other hand, for pregnant women, the SMPG was measured 60 minutes after main meal and the IAsp doses were optimized at investigator's discretion based on the subject's SMPG values with target value (less than or equal to) ≤7.8 mmol/L.

Reporting group title	IDet

Reporting group description:

Subjects were to receive IDet once or twice daily in combination with IAsp 2-4 times daily with meals as subcutaneous injection using FlexPen pen injector. The dose adjustments were made with a glycaemic target of 4.0 – 5.0 mmol/L. Dose adjustments: for IDet once daily - based on mean of 3 pre-breakfast SMPG values; for IDet twice daily - morning doses - based on mean pre-main evening meal SMPG values whereas the evening doses - based on mean pre-breakfast SMPG values. If one of the pre-main evening meal SMPG values were below target of 4.0 mmol/L, the insulin dose was reduced: <3.1 mmol/L: -4U and 3.1 – 3.9 mmol/L: -2U. If the mean was: 4.0-5.0 mmol/L- no adjustment; 5.1 – 10.0 mmol/L: +2U, 10.1 – 15.0 mmol/L: +4U and >15.0 mmol/L: +6U. For pregnant, the SMPG was measured 60 minutes after main meal and the IAsp doses were optimized at investigator's discretion based on the subject's SMPG values with target value ≤7.8 mmol/L.

Primary: Last planned glycosylated haemoglobin (HbA1c) prior to delivery

End point title	Last planned glycosylated haemoglobin (HbA1c) prior to delivery

End point description:

Mean of HbA1c at last planned visit prior to delivery after GW16 is presented. The endpoint was evaluated based on the data from both in-trial and on-treatment observation periods. In-trial observation period starts at randomization and ends at the date of trial completion. The date of trial completion is the date of the final scheduled follow-up visit V92 (delivery + 58 days). For subjects not attending the follow-up visit V92, the date of trial completion is the date of the last subject-investigator contact. On-treatment observation period starts at the date of first dose of trial product and ended at the date of the last day on trial product. Full analysis set for pregnant women (FASpregnant) included all randomised women who were pregnant during the trial. In the report data, Number of Subjects Analysed = number of subjects who contributed to the analysis and 'n' is number subjects assessed during in-trial and on-treatment observation periods.

End point type	Primary

End point timeframe:

After gestational week 16

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	84		
Units: Percentage point of HbA1c				
arithmetic mean (standard deviation)				
In-trial n = 84 (IDeg), 84 (IDet)	6.30 (± 0.70)	6.26 (± 0.73)		
On-treatment n = 83 (IDeg), 80 (IDet)	6.32 (± 0.69)	6.26 (± 0.71)		

Statistical analyses

Statistical analysis title	IDeg vs IDet

Statistical analysis description:

Primary Estimand.
Imputation of missing data was done within two groups of participants defined by randomised treatment arm based on a multiple imputation approach (x1000). For each of the 1000 imputed datasets last planned HbA1c prior to delivery after GW 16 was analysed using an ANCOVA with treatment, region and the stratification factor as categorical fixed effects and a pregnancy status at randomisation-by-baseline HbA1c interaction.

Comparison groups	IDeg v IDet
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.08

Notes:

[1] - The upper limit of the 95% CI for the estimated mean treatment difference in HbA1c was below the prespecified non-inferiority margin of 0.4%.

Statistical analysis title	IDeg vs IDet

Statistical analysis description:

Secondary Estimand.
Imputation of missing data was done within two groups of subjects defined by randomised treatment arm based on a multiple imputation approach (x1000). The imputation model included region and the stratification factor as categorical fixed effects, and a pregnancy status at randomisation-by-baseline HbA1c interaction. For each of the 1000 imputed datasets last planned HbA1c prior to delivery after GW 16 was analysed using an ANCOVA.

Comparison groups	IDeg v IDet
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.3881
Method	ANCOVA
Parameter estimate	Mean treatment difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.11

Notes:

[2] - The upper limit of the 95% CI for the estimated mean treatment difference in HbA1c was below the prespecified non-inferiority margin of 0.4%.

Secondary: HbA1c ≤ 6.0% (42 millimoles per mole (mmol/mol)) from last planned HbA1c prior to delivery (yes/no)

End point title	HbA1c ≤ 6.0% (42 millimoles per mole (mmol/mol)) from last planned HbA1c prior to delivery (yes/no)

End point description:

Number of subjects who achieved pre-defined HbA1c targets ≤ 6.0% during the in-trial pregnancy period is presented. In the reported data, 'Yes' infers number of subjects who have achieved ≤ 6.0% HbA1c whereas 'No' infers number of subjects who have not achieved ≤ 6.0% HbA1c. The endpoint was evaluated based on the data from in-trial observation period. In-trial observation period: from randomization to date of trial completion. The date of trial completion is the date of the final scheduled follow-up visit V92 (delivery + 58 days). For subjects not attending the follow-up visit V92, the date of trial completion is the date of the last subject-investigator contact. FASpregnant included all randomised women who were pregnant during the trial. In the report data, Number of Subjects Analysed = number of subjects who contributed to the analysis.

End point type	Secondary

End point timeframe:

After gestational week 16

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	84		
Units: Subjects				
Yes	36	31		
No	48	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Last planned average post-prandial glucose prior to delivery. Average of three main meals

End point title	Last planned average post-prandial glucose prior to delivery. Average of three main meals

End point description:

Mean of last planned average post-prandial glucose (PPG) prior to delivery after GW 16 is presented. Average PPG is defined as the average of the available blood glucouse (BG) measurements 90 minutes after breakfast, lunch and main evening meal respectively. The endpoint was evaluated based on the data from in-trial and on-treatment observation periods. The in-trial observation period starts at randomization and ends at the date of trial completion. The date of trial completion is the date of the final scheduled follow-up visit V92. For subjects not attending the follow-up visit V92, the date of trial completion is the date of the last subject-investigator contact. On-treatment observation period starts at the date of first dose of trial product and ended at the date of the last day on trial product. FASpregnant included all randomised women who were pregnant during the trial. In the report data, Number of Subjects Analysed = number of subjects who contributed to the analysis.

End point type	Secondary

End point timeframe:

After gestational week 16

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	83		
Units: mmol/L				
arithmetic mean (standard deviation)				
in-trial	7.37 (± 1.35)	6.96 (± 1.63)		
on-treatment	7.37 (± 1.35)	6.96 (± 1.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Last planned fasting plasma glucose prior to delivery

End point title	Last planned fasting plasma glucose prior to delivery

End point description:

Mean of last planned fasting plasma glucose (FPG) prior to delivery after GW 16 is presented. The endpoint was evaluated based on the data from in-trial and on-treatment observation periods. The in-trial observation period starts at randomization and ends at the date of trial completion. The date of trial completion is the date of the final scheduled follow-up visit V92 (delivery + 58 days). For subjects not attending the follow-up visit V92, the date of trial completion is the date of the last subject-investigator contact. On-treatment observation period starts at the date of first dose of trial product and ended at the date of the last day on trial product. FASpregnant included all randomised women who were pregnant during the trial. In the report data, Number of Subjects Analysed = number of subjects who contributed to the analysis.

End point type	Secondary

End point timeframe:

After gestational week 16

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	83		
Units: mmol/L				
arithmetic mean (standard deviation)				
in-trial	6.17 (± 2.05)	6.79 (± 2.47)		
on-treatment	6.19 (± 2.06)	6.78 (± 2.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hypoglycaemic episodes

End point title	Number of hypoglycaemic episodes

End point description:

Hypoglycaemic episode (plasma glucose <= 3.9 mmol/L (70 mg/dL) Or > 3.9 mmol/L (70 mg/dL) occurring in conjunction with hypoglycaemic symptoms) is defined as treatment emergent if the onset of the episode occurs on or after the first day of trial product administration, and no later than 7 days from the last day on trial product. Number of treatment emergent hypoglycaemic episodes during the pregnancy period is presented. The endpoint was evaluated based on the data from pregnancy period. Pregnancy period started from first day of pregnancy (date of conception corresponding to the first day in GW 2) or randomisation (whichever comes last) to the date of delivery. Safety analysis set for pregnant women (SASpregnant) included all randomised women exposed to at least one dose of trial product and who are pregnant during the trial.

End point type	Secondary

End point timeframe:

During the pregnancy period (from first day of pregnancy (date of conception) or randomisation (whichever comes last) to delivery)

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	94		
Units: Episodes				
number (not applicable)	5431	5982		

Statistical analyses

No statistical analyses for this end point

Secondary: Development of sight-threatening retinopathy defined as proliferative retinopathy or maculopathy (yes/no)

End point title	Development of sight-threatening retinopathy defined as proliferative retinopathy or maculopathy (yes/no)

End point description:

Sight-threatening retinopathy is defined as proliferative retinopathy or maculopathy. Eye examination was performed by fundus photography or pharmacologically dilated fundoscopy to identify if pregnant subjects have developed sight-threatening retinopathy. Number of subjects who developed sight-threatening retinopathy from treatment baseline as well as from pregnancy baseline to the end of treatment (EOT) visit is presented. In the reported data, 'Yes' infers number of subjects who developed sight-threatening retinopathy whereas 'No' infers number of subjects who have not developed sight-threatening retinopathy. For subjects randomised pregnant the pregnancy baseline is same as treatment baseline. For subjects randomised nonpregnant and becoming pregnant in the conception period of trial, pregnancy baseline corresponds to data from visit 55 (week 53+30 days). SASpregnant included all randomised women exposed to at least one dose of trial product and who are pregnant during the trial.

End point type	Secondary

End point timeframe:

From treatment baseline as well as from pregnancy baseline to the end of treatment visit

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	94		
Units: Subjects				
From treatment baseline to EOT: Left eye: Yes	2	2		
From treatment baseline to EOT: Left eye: No	79	79		
From treatment baseline to EOT: Left eye: Missing	10	13		
From treatment baseline to EOT: Right eye: Yes	2	2		
From treatment baseline to EOT: Right eye: No	79	79		
From treatment baseline to EOT: Right eye: Missing	10	13		
From pregnancy baseline to EOT: Left eye: Yes	2	2		
From pregnancy baseline to EOT: Left eye: No	79	79		
From pregnancy baseline to EOT: Left eye: Missing	10	13		
From pregnancy baseline to EOT: Right eye: Yes	2	2		
From pregnancy baseline to EOT:Right eye: No	79	79		
From pregnancy baseline to EOT: Right eye: Missing	10	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events during the pregnancy period

End point title	Number of adverse events during the pregnancy period

End point description:

Number of adverse events (AEs) during pregnancy period is reported. An AE was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. All AEs presented are treatment-emergent AEs (TEAEs). The TEAE is defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. SASpregnant included all randomised women exposed to at least one dose of trial product and who are pregnant during the trial.

End point type	Secondary

End point timeframe:

From first day of pregnancy (date of conception) or randomisation (whichever comes last) to delivery

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	94		
Units: Events				
number (not applicable)	429	328		

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-eclampsia defined as new-onset hypertension and simultaneous proteinuria or presence of eclampsia, haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, or other severe organ involvement (yes/no)

End point title	Pre-eclampsia defined as new-onset hypertension and simultaneous proteinuria or presence of eclampsia, haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, or other severe organ involvement (yes/no)

End point description:

Number of subjects with one or more events of pre-eclampsia during pregnancy period is reported. Pre-eclampsia was defined as new-onset hypertension (BP greater than or equal to (≥) 140 mmHg systolic or ≥ 90 mmHg diastolic, based on at least 2 measurements taken at least 4 hours apart) occurring from GW 20 to delivery and simultaneous proteinuria (defined as ≥ 300 mg protein in a 24 hours urine sample, a protein-to-creatinine ratio of ≥ 300 mg/g in a urine sample or a urine dipstick protein of 1+) or presence of eclampsia, HELLP syndrome, or other severe organ involvement. In the reported data, 'Yes' infers number of subjects who had pre-eclampsia events whereas 'No' infers number of subjects who have not had pre-eclampsia events. SASpregnant included all randomised women exposed to at least one dose of trial product and who are pregnant during the trial.

End point type	Secondary

End point timeframe:

occurring from gestational week 20 to delivery

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	94		
Units: Subjects				
Yes	12	7		
No	79	87		

Statistical analyses

No statistical analyses for this end point

Secondary: Birth weight in gram (g)

End point title	Birth weight in gram (g)

End point description:

Mean birth weight for live birth infants is presented. The endpoint was evaluated based on the data from in-trial observation period which started at randomization and ended at the date of trial completion. The

date of trial completion was the date of the final scheduled follow-up visit (delivery + 58 days). For subjects who had not attended the follow-up visit, the date of trial completion was the date of the last subject-investigator contact. FASpregnant included all randomised women who were pregnant during the trial. In the report data, Number of Subjects Analysed = number of subjects who contributed to the analysis.

End point type	Secondary

End point timeframe:

At birth

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	84		
Units: gram				
arithmetic mean (standard deviation)	3691.0 (± 628.01)	3490.2 (± 629.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-term delivery (delivery < 37 completed gestational weeks) (yes/no)

End point title	Pre-term delivery (delivery < 37 completed gestational weeks) (yes/no)

End point description:

Number of pregnant women who had pre-term delivery is presented. Pre-term delivery refers to delivery in less than 37 completed gestational weeks. In reported data, 'Yes' infers number of subjects who had pre-term delivery whereas 'No' infers number of subjects who has not had pre-term delivery. Unaddressed category refers to cases where either parents of infant had not given consent to share information after delivery or subjects who were withdrawn from trial and they did not give any further information or if subjects did not fill pregnancy outcome form. Endpoint was evaluated based on data from in-trial observation period which started at randomisation and ended at date of trial completion. Date of trial completion was date of final scheduled follow-up visit (delivery + 58 days). For subjects who had not attended follow-up visit, date of trial completion was date of last subject-investigator contact. FASpregnant included all randomised women who were pregnant during the trial.

End point type	Secondary

End point timeframe:

At birth

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	96		
Units: Subjects				
Yes	34	26		
No	57	66		
Unaddressed	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of major abnormalities (classified according to European Concerted Action on Congenital Anomalies and Twins (EUROCAT)) (yes/no)

End point title	Presence of major abnormalities (classified according to European Concerted Action on Congenital Anomalies and Twins (EUROCAT)) (yes/no)

End point description:

Number of subjects who delivered foetuses/infants with abnormalities (classified according to EUROCAT) is presented. Presence of major abnormalities were based on adjudicated data, as after adjudication congenital anomalies were classified into major abnormalities or minor anomalies or in other categories. In reported data, 'Yes' infers presence of major abnormalities whereas 'No' infers no presence of major abnormalities. FASpregnant included all randomised women who were pregnant during the trial.

End point type	Secondary

End point timeframe:

At birth

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	96		
Units: Subjects				
Yes	8	8		
No	84	88		

Statistical analyses

No statistical analyses for this end point

Secondary: Live born infants (yes/no)

End point title	Live born infants (yes/no)

End point description:

Number of subjects with live born infants is presented. In the reported data, 'Yes' infers number of live infants whereas 'No' infers early foetal death or termination of pregnancy (induced/elective abortion). Unaddressed category refers to the cases where either the parents of the infant had not given consent to share information after delivery or the subjects who were withdrawn from trial and they did not give any further information or if the subjects did not fill the pregnancy outcome form. FASpregnant included all randomised women who were pregnant during the trial.

End point type	Secondary

End point timeframe:

At birth

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	96		
Units: Subjects				
Yes	86	85		
No	5	7		
Unaddressed	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events in the infant

End point title	Number of adverse events in the infant

End point description:

AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. AEs in foetus/infant with particular focus on the AEs from delivery to follow-up are presented.

End point type	Secondary

End point timeframe:

From delivery to final follow-up

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	94		
Units: Events				
number (not applicable)	164	150		

Statistical analyses

No statistical analyses for this end point

Secondary: Neonatal hypoglycaemic episodes defined as plasma glucose ≤ 1.7 mmol/L (31 Milligrams per decilitre (mg/dL)) during the first 24 hours after birth or ≤ 2.5 mmol/L (45 mg/dL) between 24 hours and 48 hours after birth (yes/no)

End point title	Neonatal hypoglycaemic episodes defined as plasma glucose ≤ 1.7 mmol/L (31 Milligrams per decilitre (mg/dL)) during the first 24 hours after birth or ≤ 2.5 mmol/L (45 mg/dL) between 24 hours and 48 hours after birth (yes/no)

End point description:

Number of infants with neonatal hypoglycaemic episodes during the first 24 hours and between 24 hours and 48 hours after birth is presented. If plasma glucose was ≤ 1.7 mmol/L (31 mg/dL) during the first 24 hours and ≤ 2.5 mmol/L (45 mg/dL) between 24 hours and 48 hours after birth, it was called as neonatal hypoglycaemic episode. In the reported data, 'Yes' infers number of infants with neonatal hypoglycaemic episodes whereas 'No' infers number of infants with no neonatal hypoglycaemic episodes. Unaddressed category refers to the cases where either the parents of the infant had not given consent to share information after delivery or the subjects who were withdrawn from trial and they did not give any further information or if the subjects did not fill the pregnancy outcome form. FASpregnant included all randomised women who were pregnant during the trial. In the report data, Number of Subjects Analysed = number of subjects who contributed to the analysis.

End point type	Secondary

End point timeframe:

During the first 24 hours after birth or between 24 hours and 48 hours after birth

End point values	IDeg	IDet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	85		
Units: Subjects				
First 24 hours after birth: Yes	20	19		
First 24 hours after birth: No	64	65		
First 24 hours after birth: Unaddressed	2	1		
24 - 48 hours after birth: Yes	4	5		
24 - 48 hours after birth: No	77	78		
24 - 48 hours after birth: Unaddressed	5	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first day of study drug administration until final follow-up (maximum 25 months)

Adverse event reporting additional description:

All adverse events are TEAEs. A TEAE is defined as event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomized treatment. SAS all included all randomised women exposed to at least one dose of trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	IDet

Reporting group description:

Individually adjusted IDet injected subcutaneously as basal insulin once daily or twice daily + individually adjusted IAsp injected subcutaneously as bolus insulin 2-4 times daily with meals from randomization (gestational week 8-13 + 6 days) and continued until 28 days after delivery. If a subject was not pregnant at randomization, treatment was given up to a maximum of 53 weeks. For subjects who became pregnant, randomized treatment was continued throughout the pregnancy until end of treatment 28 days after delivery. Subjects who were not pregnant at 53 weeks after randomization were withdrawn.

Reporting group title	IDeg

Reporting group description:

Individually adjusted IDeg injected subcutaneously as basal insulin once daily + individually adjusted IAsp injected subcutaneously as bolus insulin 2-4 times daily with meals from randomization (gestational week 8-13 + 6 days) and continued until 28 days after delivery. If a subject was not pregnant at randomization, treatment was given up to a maximum of 53 weeks. For subjects who became pregnant, randomized treatment was continued throughout the pregnancy until end of treatment 28 days after delivery. Subjects who were not pregnant at 53 weeks after randomization were withdrawn.

Serious adverse events	IDet	IDeg	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 112 (33.93%)	41 / 110 (37.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Diabetes mellitus management			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maternal therapy to enhance foetal lung maturity			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	2 / 112 (1.79%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	2 / 112 (1.79%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion threatened			
subjects affected / exposed	2 / 112 (1.79%)	3 / 110 (2.73%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anembryonic gestation			
subjects affected / exposed	1 / 112 (0.89%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cervical incompetence			
subjects affected / exposed	1 / 112 (0.89%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eclampsia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal hypokinesia			
subjects affected / exposed	1 / 112 (0.89%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational hypertension			
subjects affected / exposed	6 / 112 (5.36%)	3 / 110 (2.73%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational oedema			
subjects affected / exposed	1 / 112 (0.89%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HELLP syndrome			
subjects affected / exposed	0 / 112 (0.00%)	3 / 110 (2.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage in pregnancy			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placental insufficiency			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyhydramnios			

subjects affected / exposed	1 / 112 (0.89%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum haemorrhage			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia			
subjects affected / exposed	2 / 112 (1.79%)	6 / 110 (5.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature rupture of membranes			
subjects affected / exposed	1 / 112 (0.89%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature separation of placenta			
subjects affected / exposed	1 / 112 (0.89%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Preterm premature rupture of membranes			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Threatened labour			
subjects affected / exposed	4 / 112 (3.57%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine contractions abnormal			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine hypotonus			

subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Injection site hypersensitivity			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shortened cervix			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haematoma			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 112 (0.89%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood ketone body increased			

subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical observation			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 112 (0.89%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medication error			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 112 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Dizziness postural			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia of pregnancy			
subjects affected / exposed	2 / 112 (1.79%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diabetic retinal oedema			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular oedema			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 112 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 112 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis of pregnancy			
subjects affected / exposed	0 / 112 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	2 / 112 (1.79%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 112 (0.89%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	6 / 112 (5.36%)	4 / 110 (3.64%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	IDet	IDeg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 112 (54.46%)	76 / 110 (69.09%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 112 (8.93%)	8 / 110 (7.27%)	
occurrences (all)	16	18	
Pregnancy, puerperium and perinatal conditions			
Placental insufficiency			
subjects affected / exposed	5 / 112 (4.46%)	7 / 110 (6.36%)	
occurrences (all)	5	7	

Polyhydramnios			
subjects affected / exposed	8 / 112 (7.14%)	6 / 110 (5.45%)	
occurrences (all)	8	6	
Pre-eclampsia			
subjects affected / exposed	6 / 112 (5.36%)	4 / 110 (3.64%)	
occurrences (all)	7	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 112 (14.29%)	22 / 110 (20.00%)	
occurrences (all)	16	22	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 112 (0.89%)	8 / 110 (7.27%)	
occurrences (all)	1	9	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 112 (0.89%)	6 / 110 (5.45%)	
occurrences (all)	1	9	
Abdominal pain upper			
subjects affected / exposed	6 / 112 (5.36%)	2 / 110 (1.82%)	
occurrences (all)	8	2	
Diarrhoea			
subjects affected / exposed	1 / 112 (0.89%)	8 / 110 (7.27%)	
occurrences (all)	1	9	
Nausea			
subjects affected / exposed	7 / 112 (6.25%)	7 / 110 (6.36%)	
occurrences (all)	10	7	
Vomiting			
subjects affected / exposed	6 / 112 (5.36%)	8 / 110 (7.27%)	
occurrences (all)	8	8	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	5 / 112 (4.46%)	7 / 110 (6.36%)	
occurrences (all)	5	12	
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	7 / 112 (6.25%)	5 / 110 (4.55%)	
occurrences (all)	10	5	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	4 / 112 (3.57%)	6 / 110 (5.45%)	
occurrences (all)	4	7	
Infections and infestations			
Influenza			
subjects affected / exposed	7 / 112 (6.25%)	5 / 110 (4.55%)	
occurrences (all)	10	6	
Nasopharyngitis			
subjects affected / exposed	23 / 112 (20.54%)	21 / 110 (19.09%)	
occurrences (all)	45	30	
Pharyngitis			
subjects affected / exposed	2 / 112 (1.79%)	7 / 110 (6.36%)	
occurrences (all)	2	7	
Sinusitis			
subjects affected / exposed	6 / 112 (5.36%)	2 / 110 (1.82%)	
occurrences (all)	6	2	
Urinary tract infection			
subjects affected / exposed	9 / 112 (8.04%)	11 / 110 (10.00%)	
occurrences (all)	11	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2018	Discontinuation of the glycaemic data collection system (i.e. the combined use of a blood glucose (BG)-meter and eDiary). Instead a paper diary solution was implemented.
30 April 2019	Reduction in sample size

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported